REMARKS

Applicant respectfully requests entry of amendments to claims 1, 11, 25, 41, and 45. Please cancel claims 2, 15, 18-24, 26, 42, 43, and 47-52, without prejudice or disclaimer. Support for the amendments can be found throughout the specification, including paragraphs [0111], [0053], [0090], [0121], and [0123], and Figures 2, 5, 10, and 11, and the originally filed claims and, therefore, do not add new matter.

Applicant submits that pending claims 1, 3-14, 16, 17, 25, 27-41, and 44-46 are in condition for allowance, or are in better condition for presentation on appeal, and respectfully requests that the claims as amended be entered.

Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 1, 3-14, 16-19, 21-25, 27-41, and 43-52 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. As claims 18, 19, 21-24, 43, and 47-52 have been canceled, the rejection as applied to these claims is rendered moot.

Applicant traverses the rejection as it might apply to the amended claims, including claims dependent therefrom, for the reasons given below.

Regarding step a of claims 1, 25, and 45, the Office Action alleges, in pertinent part, that it is unclear what the chimeric DNA constructs contain beyond one of the 5' or 3' regulatory sequences. Applicant submits that as stated in Miles Laboratories, Inc. v. Shandon Inc., 27 U.S.P.Q.2d 1123 (Fed. Cir. 1993), cert denied, 510 U.S. 1100 (1994):

> "The test for definiteness is whether one skilled in the art would have understood the bounds of the claim when read in light of the specification . . .. If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, 112 demands no more . . .."

Respectfully, Applicant submits that the specification clearly apprises one of skill in the art the scope of the invention. For example, at paragraph [0089] the specification recites:

> "Figure 1A shows the PCR procedure used to generate recombinant DNA between mouse and human sequences. Two BACs carrying either mouse (BAC-1) or the human orthologue of the mouse gene (BAC-2) gene are created. The

> BACs may include the control region contiguous to the coding region. Two PCR products (pA and pB) are made, both are hybrid products between human and mouse DNA. The first half of pA is 2 kb upstream of mouse DNA from the beginning of the coding region and the second half is 2 kb human DNA starting at the first codon ATG of the human coding region. Likewise, the half of pB is 2 kb human DNA containing the last codon TAG at the junction of the second half that is 2 kb downstream of mouse DNA from the TAG."

Clearly, the skilled artisan would understand from this example that pA and pB represent the chimeric constructs recited in the claims. Further, the skilled artisan would understand from this example that, in addition to comprising 3' and 5' regulatory sequences (e.g., start and stop codons), the chimeric constructs comprise non-coding sequences of a mouse or non-human animal gene and sequences encoding the human orthologue.

In another example, at paragraph [0092], the specification recites:

> "A second round of PCR can be used to generate PCR products having DNA from both mouse and human. Figure 1C, for example, shows the use of PCR primers to generate fragments labeled Product 5 and Product 6, that have a junction between the human and mouse DNA at the ends of the coding region of the gene. As shown in Figure 1C, there is an overlapping 20 bases between 3' end of Product 1 and 5' end of Product 2. Using primers p1 and p4, and the two product[sic], PCR- 5 generate ~4kb product 5 that is a fused DNA at the overlapping region. Likewise, ~4 kb Product 6 is generated as a fused DNA between Products 3 and 4."

As in the previous example, one of skill in the art would clearly appreciate that Product 5 and Product 6 represent the chimeric constructs recited in the claims. Again, the skilled artisan would understand from this example that the chimeric constructs comprise non-coding sequences of a mouse or non-human animal gene and sequences encoding the human orthologue. Further, at paragraph [0111], the specification recites:

> "As outlined in Figures 9 to 11, the construction of a pair of head and tail chimeras, and subsequent fusion product has been completed. The head chimera

> is derived from 1,169 bp upstream region of the first codon GTG of mouse PXR and from 1,929 bp downstream region of the first codon GTG of human PXR. This chimera has been made by a two-step PCR procedure . . . the first PCR generated 1,169 bp and 1,929 bp products from corresponding regions, and the second PCR has generated the chimeric product via 40 bp overlapping segment between the two initial products. The resultant product is called 5' head chimera. Likewise, 3' tail chimera has been constructed by the fusion of 1,194 bp human and 1,223 bp mouse segments (Figure 9). The last terminator codon is at the junction of two segments as illustrated in Figure 9."

Clearly, the skilled artisan would understand from this example that 5' head chimera and 3' tail chimera represent the chimeric constructs recited in the claims. Further, the skilled artisan would also understand from this example that in addition to comprising 3' and 5' regulatory sequences (e.g., start and stop codons), the chimeric constructs comprise non-coding sequences of a mouse gene (PXR) and sequences encoding the human orthologue (PXR).

As such one of skill in the art reading the claims in light of the specification would understand that, in addition to comprising regulatory regions, the chimeric constructs as claimed would also contain sequences comprising non-coding sequences of a mouse or non-human animal gene and sequences encoding the human orthologue of the mouse or non-human animal gene. Therefore, in view of the test for definiteness recited in Miles Laboratories, nothing more is required.

Regarding step b of claims 1, 25, and 45, the Office Action alleges that "the ends of the human DNA do not comprise the at least two chimeric DNA constructs in the context of the claims, and further that it is unclear where the ends ligate to (e.g., together), and whether it's between any random chimeric DNA constructs, such as two chimeric constructs both contain a 5'-regulatory sequence." While not acquiescing to the reasoning offered in the Office Action, in order to expedite prosecution toward allowance, the claims have been amended to recite "ligating the human DNA ends of the first and second chimeric DNA constructs." Since "ligation," by

definition, means to join molecules or molecular fragments together with a bond,[1] the skilled artisan would understand the metes and bounds of the claims.

Regarding step c, the Office Action alleges that because the ligated constructs comprises human sequences flanked by mouse sequences, it is unclear how the human sequence in the third construct differs from that of the ligated chimeric DNA construct before it recombines with second construct. While not acquiescing to the reasoning offered in the Office Action, in order to expedite prosecution toward allowance, the claims have been amended to recite "thereby allowing for modification of human DNA of the ligated chimeric DNA constructs." The ligating step makes regions within the human sequence available for modification (e.g., insertion of restrictions sites, positive selection markers, and/or negative selection markers). For example, at paragraph [0112], the specification recites that 5' head and 3' tail chimera were merged to create a Cla I site (see also, Figure 10), followed by insertion of a tetA gene into the Cla I site (Figure 11). Further, as shown in Figures 2 and 6, the chimeras allow for insertion of positive and/or negative selection markers resulting in Product 7 (i.e., a ligated construct generated from two chimeras), which may be recombined to form Product 8 (i.e., third DNA construct; see, e.g., Figure 3). Again, as the test for definiteness is whether one skilled in the art would have understood the bounds of the claim when read in light of the specification, Applicant submits that one of skill in the art would understand the difference between the human sequence in the third construct and the ligated chimeric DNA construct.

For these reasons, Applicant respectfully requests that the rejection be withdrawn.

Rejections Under 35 U.S.C. §102

Claim 41 stands rejected under 35 U.S.C. §102(b), as allegedly being anticipated by Shiao et al. as evidenced by Wikipedia Receptor, 2008.

Applicant traverses the rejection as it might apply to the amended claims, including claims dependent therefrom, for the reasons given below.

---

[1] See, e.g., Oxford Dictionary of Biochemistry and Molecular Biology, Revised Ed., 2001, Oxford University Press, Inc., New York, NY.

The Office Action alleges, in pertinent part, that the cited reference teaches the elements as recited in the present claims because as 1) the claim recites a G-protein coupled receptor gene and 2) the glucagon receptor is a member of this class of protein receptors, the claim is anticipated by Shiao et al. However, the claim has been amended to recite "wherein the mouse comprises a selection marker contained within the at least one intron."

Review of Shiao et al. demonstrates that the neomycin resistance and TK genes lay outside of the human GR gene (e.g., neomycin gene is added to the end of human GR gene fragment [see p. 297, col. 1: *Targeting vector*; TK gene is ligated downstream from the mouse 3' flanking sequence [Id.]). Further, because a structural gene within a humanized mouse containing a selection marker comprised within an intron as claimed is different from a humanized mouse containing a selection marker outside of structural gene as recited in the reference, where that difference is determinable (e.g., nucleic acid probe could differentiate the two), the mouse as disclosed in the reference does not meet every element of the mouse as claimed.

As stated in Hybritech Inc. v. Monoclonal Antibody, Inc., 231 U.S.P.Q. 81 (Fed. Cir. 1986), "It is axiomatic that for prior art to anticipate under 102 it has to meet every element of the claimed invention."

Therefore, because the instant claim recites a humanized mouse comprising a selection marker within an intron, the Shiao et al. reference does not anticipate the claimed invention.

Failure of the prior art to meet every element of the claimed invention does not meet the standard under §102. For these reasons, Applicant respectfully requests that the rejection be withdrawn.

Claim 41 stands rejected under 35 U.S.C. §102(b), as allegedly being anticipated by Divoky et al. as evidenced by Wikipedia Receptor, 2008.

Applicant traverses the rejection as it might apply to the amended claims, including claims dependent therefrom, for the reasons given below.

The Office Action alleges, in pertinent part, that the cited reference teaches the elements as recited in the present claims because as 1) the claim recites a kinase gene and 2) the

erthropoietin receptor is a member of this class of protein receptors, the claim is anticipated by Divoky et al. However, the claim has been amended to recite "wherein the mouse comprises a selection marker contained within the at least one intron, and wherein the mouse is homozygous for the human DNA gene."

As stated in the amendment of November 27, 2007, Divoky et al. require the use of double replacement gene targeting (see, p. 987, col. 1, "Homologous Recombination in ES cells and Generation of hEPOR Knock-In Mice," col. 2, "Results and Discussion" (tag and exchange); and p. 988, Fig. 1). Divoky et al. teach that the ES cell is first contacted with a targeting vector to insert a positive selectable marker into ES cells. The "tagged" cells are then used to produce offspring, and those animals showing germ line transmission for the positive marker are used to produce cell lines for a second targeting vector (exchange). Once exchanged, the selection marker is removed from the recombined structural gene (see, e.g., Figure 1, p. 988).

Divoky et al. also state that they did not produce a homozygous mouse comprising a selection marker (see p. 987, col. 1, paragraph 2, "Cre-Mediated Reactivation of Hypomorphic Allele: Mice Survive Solely on hEPOR"). Thus, because the humanized mouse as claimed is homozygous for a gene comprising a selection marker in an intron, the mouse of Divoky et al. does not meet every element of the claimed invention.

As stated in Hybritech Inc. v. Monoclonal Antibody, Inc., 231 U.S.P.Q. 81 (Fed. Cir. 1986), "It is axiomatic that for prior art to anticipate under 102 it has to meet every element of the claimed invention."

Failure of the prior art to meet every element of the claimed invention does not meet the standard under §102. For these reasons, Applicant respectfully requests that the rejection be withdrawn.

Rejections Under 35 U.S.C. §103

Claims 18, 19, 21-24, and 47-52 stand rejected under 35 U.S.C. §103(a), as allegedly being unpatentable over Divoky et al. in view of Heintz et al. As claims 18, 19, 21-24, and 47-52 have been canceled, the rejection as applied to these claims is rendered moot.

For these reasons, Applicant respectfully requests that the rejection be withdrawn.

Claims 41 and 44 stand rejected under 35 U.S.C. §103(a), as allegedly being unpatentable over Divoky et al. in view of Xie et al. Applicant traverses the rejection as it might apply to the amended claims, including claims dependent therefrom, for the reasons given below.

Applicant submits that because the cited references do not teach all the claim limitations, no *prima facie* case has been established.

The deficiencies identified in Divoky et al. have been identified above, and will not be reiterated here. The Office Action alleges, in pertinent part, that Divoky et al. is silent with respect to the specific gene recited (i.e., PXR). The Action then provides Xie et al. to cure the deficiencies identified in the primary reference.

Review of Xie et al. shows that the transgenic animals comprising the PXR gene were not created by homologous recombination, and in fact, the transgenic animals are generated using cDNA and vectors comprising sequences from mouse albumin promoter/enhancer and SV40 intron polyA sequences (p. 438, col. 2, "Generation of transgenic mice"). As such, there would be no PXR non-coding regions at the 3' and 5' ends which would allow for homologous recombination. Further, as the vectors comprise cDNA, there are, for example, no introns available, thus, there would be a lack of available expression control signals for appropriate induction/suppression of expression in particular cells. Therefore, while Xie et al. may or may not teach transgenic mice comprising PXR, they do not teach homologous recombination between mice and human DNA sequences that have the same relative order when such sequences are present in the genome of a human (i.e., comprise intronic sequences). Moreover, as Divoky et al. do not teach or suggest a humanized mouse which is homozygous for a recombined gene comprising a selection marker, the combination would not result in the invention as claimed.

Again, it is axiomatic that one cannot simply use the Applicant's disclosure as a "blueprint" to reconstruct, by hindsight, Applicant's claim. See, e.g., Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 227 U.S.P.Q. 543 (Fed. Cir. 1985). Since the teachings of Divoky et al. would not result in the claimed invention when combined with the teachings of Xie et al., one of skill in the art would not have an expectation of success because the invention as claimed

would not be achieved in view of such teachings. Therefore, one of skill in the art would not be motivated to combine such teachings.

Therefore, because of the failure of Divoky et al. to teach or suggest a homozygous mouse comprising a selection marker, and because Xie et al., by virtue of using cDNA, fail to teach DNA sequences having the same relative order of sequences present on a human genome, there is no reasonable expectation of successfully achieving the claimed invention in view of the combined references, thus, no *prima facie* case for obviousness exists.

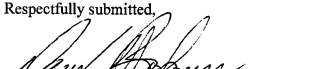
For these reasons, Applicant respectfully requests that the rejection, including as it might be applied against the amended claims, be withdrawn.

Conclusion

Applicant submits that pending claims 1, 3-14, 16, 17, 25, 27-41, and 44-46 are in condition for allowance, or are in better condition for appeal. The Examiner is invited to contact Applicant's undersigned representative if there are any questions relating to this submission.

No fee is deemed necessary with the filing of this paper. However, the Commissioner is hereby authorized to charge any fees required by this submission, or credit any overpayments, to Deposit Account No. 07-1896 referencing the above-identified docket number.

Respectfully submitted,



Date: May 23, 2008

Daryl A. Basham, J.D., Ph.D.
Registration No. 45,869
Telephone: (858) 677-1429
Facsimile: (858) 677-1465

DLA Piper US LLP
4365 Executive Drive, Suite 1100
San Diego, California 92121-2133
USPTO Customer Number 28213